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Opinoin

Emerging Roles of Skeletal Muscle-Derived Exosomal miRNAs in Metabolic Regulation: A Perspective

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ABSTRACT: Skeletal muscle (SKM) is now recognized not only for its classical functions but also as a secretory organ. It communicates with other tissues through myokines and extracellular vesicles， such as exosomes. Among these components, microRNAs (miRNAs) are particularly notable due to their stability, evolutionary conservation, and ability to potently regulate gene expression. Growing evidence suggests that these exosomal miRNAs act as important mediators of inter-organ communication in both glucose and lipid metabolism. Exosomal miRNAs derived from senescent SKMs drive systemic metabolic dysregulation by targeting critical signaling pathways in insulin sensitivity and lipid metabolism. Consequently, SKM-derived exosomal miRNAs have emerged as a promising new class of biomarkers and therapeutic targets for metabolic diseases.

Keywords: skeletal, muscle, exosomal, miRNAs, metabolic

INTRODUCTION

Skeletal muscle (SKM) is a striated muscle under voluntary control that was traditionally thought to be responsible for body movement, postural maintenance, and heat production. However, recent studies have revealed that SKM also functions as a secretory organ, synthesizing and releasing various myokines through endocrine, paracrine, and autocrine pathways to facilitate intercellular communication [1]. In addition, extracellular vesicles (EVs) have emerged as vital bioactive mediators in tissue crosstalk. Exosomes are small EVs with a diameter of approximately 30-150 nm, are formed through the inward budding of the limiting membrane of multivesicular bodies [2]. Their biogenesis begins with the formation of early endosomes through the endocytosis of the plasma membrane [3]. The specific composition and involvement of SKM-derived exosomal miRNAs in glucose metabolism are detailed in Figure 1. The quantity and biological functionality of exosomes secreted by SKM are profoundly influenced by its metabolic activity [4]. And a reduction in SKM mass leads to a decrease in both the output and bioactivity of its secreted exosomes [5]. Secreted into various body fluids, exosomes are enriched with diverse bioactive cargo, including proteins, nucleic acids, and lipids, which can be delivered to recipient cells to transmit molecular signals. Exosomal nucleic acids include mRNAs and noncoding RNAs such as microRNAs (miRNAs), lncRNAs, and circRNAs [6]. The miRNAs in exosomes have attracted particular attention because they are highly conserved across species and have broad regulatory effects on gene expression [7]. Upon release, SKM-derived exosomal miRNAs are taken up by target cells through endocytosis or membrane fusion, thereby mediating intercellular and inter-organ communication. The current research suggests that exercise (such as aerobic, resistance, and eccentric training), dietary/lipid stimulation, and neural regulation collectively regulate the quantity and variety of SKM-derived exosomal miRNAs [8–10]. Notably, one study suggested that miRNAs may mediate approximately 70% of the regulatory effects exerted by exosomes on target

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cells, far surpassing the contribution of proteins, which account for only about 10% [11]. Despite the growing body of research on exosomal miRNAs, a systematic understanding of the role of SKM-derived exosomal miRNAs in metabolic diseases remains limited. Given the accumulating evidence for their role in inter-tissue communication, we propose that SKM-derived exosomal miRNAs represent a key communication mechanism that regulates glucose and lipid metabolism, and that also represent a novel class of predictive biomarkers and therapeutic targets for various metabolism-related diseases, including type 2 diabetes, hyperlipidemia, stroke, myocardial infarction, fatty liver disease, and metabolic syndrome.

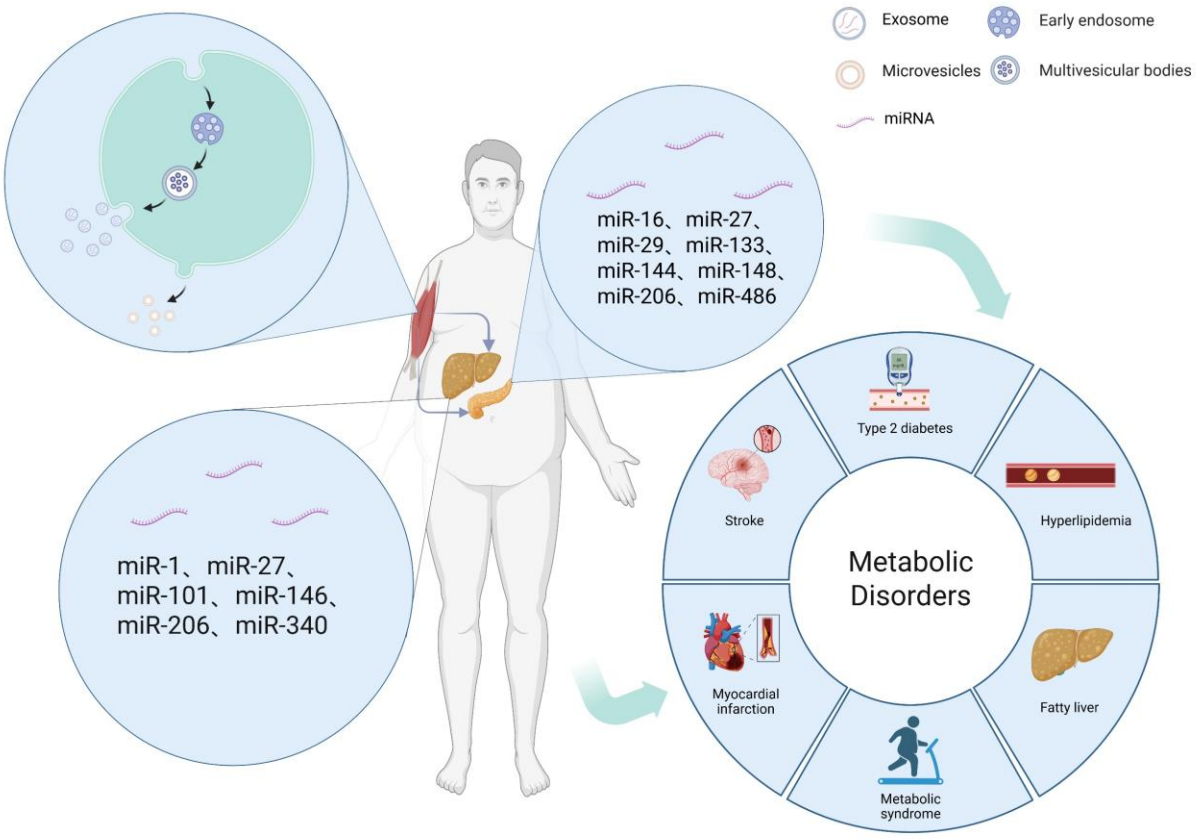

Figure 1. The involvement of skeletal muscle-derived exosomal miRNAs in glucose and lipid metabolism processes. Skeletal muscle-derived exosomes are small extracellular vesicles with a diameter of approximately 30-150 nm, which are formed by the inward budding of the membrane of multivesicular bodies. Their biogenesis begins with the formation of early sorting endosomes through the endocytosis of the plasma membrane. Furthermore, these exosomal miRNAs modulate glucose and lipid metabolism within key metabolic organs, including the liver and pancreas. Owing to their critical regulatory roles, they represent a novel class of predictive biomarkers and promising therapeutic targets for a spectrum of metabolism-related diseases, including type 2 diabetes, hyperlipidemia, stroke, myocardial infarction, fatty liver disease, and metabolic syndrome.

Evidence and mechanisms of SKM－derived exosomal miRNAs in glucose metabolism

We identified several skeletal muscle-derived exosomal miRNAs that function as critical regulators of metabolism. Specifically, these miRNAs exert their effects by fine-tuning important pathways such as the PI3K (phosphatidylinositol3-kinase)-protein kinase B (Akt)-mechanistic target of rapamycin (mToR) and peroxisome proliferator-activated receptor gamma (PPARγ) signaling, thereby influencing outcomes ranging from glucose uptake and insulin sensitivity to adipocyte differentiation and lipolysis (Table 1). The uptake of SKM-EVs by pancreatic beta cells underlines their potential role in regulating glucose homeostasis and the development of diabetes [12]. For instance, SKM-derived exosomal miR-486 inhibits phosphatase and tensin homolog (PTEN), which may enhances insulin signaling and activates the insulin-like growth factor 1 (IGF-1)/ Akt/mToR pathway, ultimately leading to increased glucose uptake and protein synthesis [13]. Research in mice indicates that SKM-derived exosomal miR-16 is delivered to the pancreas, where it suppresses Patched 1 (PTCH1) expression, thereby altering the β-cell signaling

network, modulating islet size and ultimately affecting β-cell proliferation and secretion (Fig. 2) [14]. This inter-tissue communication is not limited to the pancreas. Exercise is a powerful stimulus for the release of exosomes into circulation. Castano et al. [8] found that high-intensity interval training induces the release of exosomes containing miR-133a and miR-133b from mouse SKM. Upon uptake by the liver, these exosomes downregulate Forkhead box protein O1 (FOXO1), thereby inhibiting the expression of gluconeogenic genes such as Glucose-6-phosphatase catalytic subunit (G6pc), reducing endogenous glucose production, and improving glucose tolerance and insulin sensitivity. Furthermore, injecting exosomes isolated from the plasma of exercised mice into sedentary mice significantly improved their glucose tolerance and insulin sensitivity. Although exosome-injection experiments have suggested a functional effect, the necessity of this effect remains to be confirmed by *in vivo* studies that specifically knock down or overexpress individual miRNAs. These findings strongly suggest that SKM-derived exosomal miRNAs mediate the beneficial systemic metabolic effects of exercise. The translational relevance of these findings is supported by human studies. The expression of six SKM-derived exosomal miRNAs (miR-133b-3p, miR-206, miR-27a-3p, miR-29a-3p, miR-29b-3p, and miR-29c-3p) differed between type 2 diabetic and non-diabetic overweight/obese individuals; among which, miR-27a-3p and the miR-29 family members were significantly negatively correlated with insulin sensitivity [15]. Further elucidating the molecular mechanisms, studies in human myotubes have shown that increased expression of miR-148b reduces neuroblastoma RAS viral oncogene homolog (NRAS) and Rho-associated coiled-coil containing protein kinase 1 (ROCK1) protein levels and attenuates insulin-induced Akt phosphorylation and glucose uptake [16]. Notably, while SKM rarely releases miRNAs such as miR-1, miR-133a, miR-133b, miR-206, miR-208b, and miR-499 into the circulation in healthy young individuals [17], their release appears to be dysregulated in disease states. For example, elevated SKM-derived exosomal miR-144 in type 2 diabetes, which inversely correlates with insulin receptor substrate 1 (IRS-1) expression, suggests its role in the pathogenesis of insulin resistance [17]. Additional information is provided in Figure 2. Collectively, these discoveries highlight the dysregulation of SKM-derived exosomal miRNAs in metabolic disease. However, interspecies differences and heterogeneity under pathological conditions may also compromise the validity of these conclusions.

Table 1. The mechanisms of skeletal muscle-derived exosomal miRNAs in metabolic regulation through specific target genes and pathways.

miRNA	Study	Year	Experimental subjects	Change of expression	Verified target genes/pathways	Metabolic effects
miR-486	Aoiet al	2021	Mouse	Upregulated	Inhibition of PTEN activates the PI3K-Akt-mTOR pathway	Promotes glucose uptake and protein synthesis
miR-16	Barlow et al	2018	Mouse	Upregulated	Inhibition of PTCH1 activates the β-cell signaling network	Promotes β-cell proliferation and secretion
miR-133a/b	Castaño et al	2020	Mouse	Upregulated after high-intensity interval training	Inhibition of FOXO1 suppresses hepatic gluconeogenesis (eg, G6pc)	Enhances insulin sensitivity
miR-148b	Gastebois et al	2016	Human	Upregulated	Inhibition of NRAS and ROCK1 attenuates Akt phosphorylation	Inhibits glucose uptake
miR-144	Aoi and Sakuma	2014	Human	Upregulated in type 2 diabetes patients	Inhibition of IRS-1	Promotes insulin resistance
miR-146a-5p	Qin et al; Li et al	2023/ 2021	Mouse, Pig	Upregulated	Inhibition of GDF5 suppresses the PPARγ signaling pathway	Adipocyte differentiation, lipid accumulation, and lipid/glucose uptake
miR-1	Guo et al	2023	Mouse, Human	Downregulated during aging	Suppression of β3-AR expression	Suppresses adrenergic signaling and lipolysis
miR-34a	Kukreti et al	2020	Mouse	Upregulated	Inhibition of CERK leads to sphingolipid accumulation and subsequent activation of the PP2A/JNK pathway	Impairs insulin signal transduction
miR-431	Lee et al	2015	Mouse	Downregulated during aging	Inhibition of SMAD4 attenuates	Indirectly affects insulin resistance or lipid metabolism

Abbreviation: β-3-adrenergic receptor (β 3-AR), Ceramide kinase (CERK), Forkhead box protein O1 (FOXO1), Glucose-6-phosphatase catalytic subunit (G6PC), Growth differentiation factor 5 (GDF5), Insulin-like growth factor 1 (IGF-1), Insulin receptor substrate 1 (IRS-1), c-Jun N-terminal Kinase (JNK), Mechanistic target of rapamycin (mTOR), microRNA (miRNA), Neuroblastoma RAS viral oncogene homolog (NRAS), Patched 1 (PTCH1), PI3K (phosphatidylinositol3-kinase), Peroxisome proliferator-Activated Receptor Alpha (PPARα), Peroxisome proliferator-activated receptor gamma (PPARγ), Phosphatase and tensin homolog (PTEN), PPAR Gamma Coactivator 1-Alpha (PGC1a), Protein phosphatase 2A (PP2A), Protein kinase B (Akt), Rho-associated coiled-coil containing protein kinase 1 (ROCK1), Mothers against decapentaplegic homolog 4 (SMAD4).

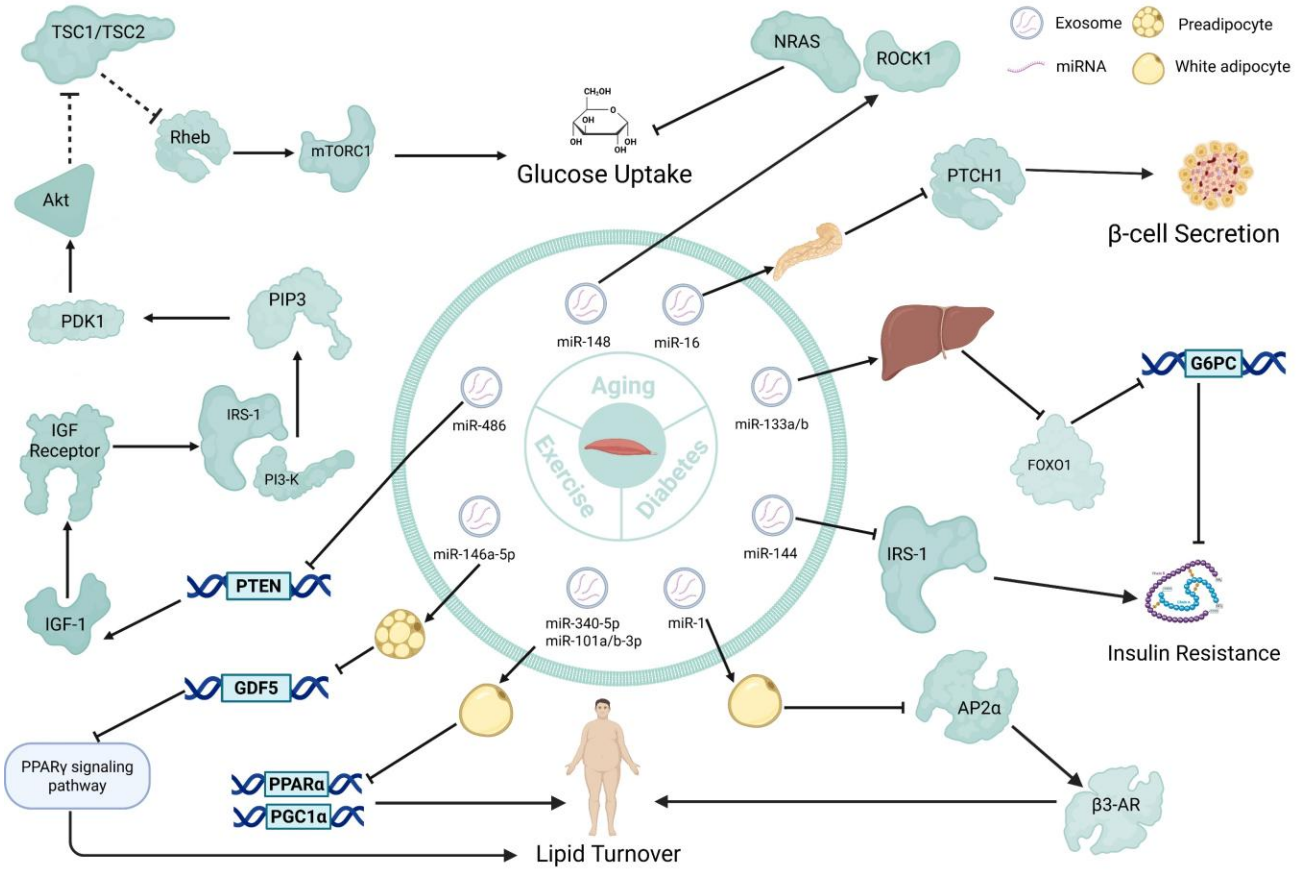

Figure 2. Mechanism of skeletal muscle-derived exosomal miRNAs in systemic glucose and lipid metabolism regulation. Different types of skeletal muscle-derived exosomal miRNAs (such as miR-1, miR-16, miR-27a-3p, miR-29, miR-101a/b-3p, miR-133a/b, miR-144, miR-146a-5p, miR-148, miR-340-5p, miR-486) reach target organs or cells such as pancreatic β-cells, adipocytes, and the liver. Through various signaling pathways, they influence β-cell proliferation and insulin secretion, glucose uptake, lipid turnover and insulin resistance, thereby exerting regulatory effects on metabolism. **Abbreviation:** Activator protein 2 alpha (AP-2α), β-3-adrenergic receptor (β3-AR), Forkhead box protein O1 (FOXO1), Glucose-6-phosphatase catalytic subunit (G6PC), Growth differentiation factor 5 (GDF5), Insulin-like growth factor 1 (IGF-1), Insulin-like growth factor receptor (IGF Receptor), Insulin receptor substrate 1 (IRS-1), Mechanistic target of rapamycin (mTOR), Mechanistic target of rapamycin complex 1 (mTORC1), microRNA (miRNA), Neuroblastoma RAS viral oncogene homolog (NRAS), Patched 1 (PTCH1), Peroxisome proliferator-Activated Receptor Alpha (PPARα), Peroxisome proliferator-activated receptor gamma (PPARγ), Phosphatidylinositol 3-kinase (PI3K), Phosphatidylinositol-3,4,5-trisphosphate (PIP3), Phosphoinositide-dependent kinase 1 (PDK1), Phosphatase and tensin homolog (PTEN), PPAR Gamma Coactivator 1-Alpha (PGC1a), Protein kinase B (Akt), Rho-associated coiled-coil containing protein kinase 1 (ROCK1), Ras homolog enriched in brain (Rheb), Tuberous sclerosis complex 1/Tuberous sclerosis complex 2 (TSC1/TSC2),

Evidence and mechanisms of SKM–derived exosomal miRNAs in lipid metabolism

SKM-derived exosomal miRNAs are critical mediators of muscle-adipose tissue crosstalk. Through endocrine and paracrine pathways, they regulate metabolic processes in adipocytes, thereby influencing whole-body energy homeostasis. Qin et al. [18]. discovered that miR-146a-5p is highly enriched in SKM-derived exosomes and can be taken up by preadipocytes. Upon uptake, it suppresses the PPARγ signaling pathway by targeting the growth differentiation factor 5 (GDF5) gene. GDF5 is a positive regulator of the PPARγ signaling pathway, a master regulator of adipogenesis. The downregulation of GDF5 by miR-146a-5p consequently inhibits the PPARγ signaling pathway. This inhibition is evidenced by the reduced expression of PPARγ and its downstream target genes, including C/EBPα, CD36, FABP4, and FASN (Fig. 2). thereby inhibiting adipocyte differentiation, lipid accumulation, and lipid/glucose uptake. SKM specific knockout of miR-146a-5p led to increased body weight and adipose tissue mass in mice, whereas injecting

exosomes rich in miR-146a-5p reversed these phenotypes. Studies in pigs have corroborated these findings, confirming the role of SKM-derived exosomal miR-146a-5p [19]. Although consistency across species strengthens the reliability of the findings, these mechanisms still need to be validated in human studies. Importantly, the dysregulation of specific SKM-derived exosomal miRNAs in obesity can disrupt this metabolic balance. A study found that in the SKM exosomes of obese mice, miR-340-5p, miR-1a-3p, miR-101a-3p, and miR-101b-3p were significantly downregulated.

Since these miRNAs are predicted to target and inhibit key regulators of fatty acid metabolism pathways, such as Peroxisome Proliferator-Activated Receptor Alpha (PPARα) and PPAR Gamma Coactivator 1-Alpha (PGC1α)，their reduction may lead to a weakened suppression of fatty acid metabolism [20]. Beyond these global changes, certain SKM-derived exosomal miRNAs directly target adipogenic processes. For instance, SKM-derived exosomal miR-1 can fuse with white adipocytes and, by targeting the transcription factor activator protein 2 alpha (AP-2α), upregulate the expression of β-3-adrenergic receptor (β3-AR), thereby promoting adrenergic signaling and lipolysis [21]. In summary, SKM-derived exosomes modulate lipid metabolism in recipient adipocytes and myocytes via miRNAs, thereby coordinating processes such as lipid storage, fatty acid uptake, and oxidation, and underscoring their crucial role in the metabolic crosstalk between SKM and adipose tissue. These findings have primarily established a correlation between altered miRNA expression and metabolic phenotypes, yet the definitive causal relationship requires further validation through gain and loss of function experiments.

Exosomal miRNAs from aged SKM drive metabolic dysfunction

During the human aging process, the mass, quantity, and function of SKM undergo corresponding changes, a condition termed sarcopenia. This common geriatric syndrome is associated with increased risks of frailty, disability, and metabolic disorders, the epidemiology and adverse outcomes of which are now widely recognized [22]. Related research has identified myokine imbalance, chronic inflammation, vitamin D deficiency, and insulin resistance in aging SKM as central contributors to metabolic disorders [21, 23]. However, the precise molecular mechanisms involved remain elusive. We hypothesize that SKM-derived exosomal miRNAs may serve as critical mediators linking muscular aging to metabolism. Notably, SKM aging is associated with a reduction in exosome release and significant alterations in their miRNA cargo. These changes not only impair intramuscular homeostasis but also exacerbate systemic metabolic dysregulation by disrupting inter-organ communication, thereby increasing the risk of metabolic diseases. Exosome-like vesicles released by aged human myotubes (P30 high-passage model) displayed markedly reduced levels of Alix, Syntenin-1 and α-sarcoglycan, suggesting compromised exosome biogenesis and secretion in senescent skeletal-muscle cells [24]. Numerous studies have demonstrated that aging SKM shows a consistent pattern of downregulation in miR-1, miR-206, miR-431, and miR-451, alongside an upregulation in miR-34a and miR-434-3p [13, 24–29].

Consequently, such disturbances destabilize muscle homeostasis and can relay metabolic dysregulation to distal organs. RNA sequencing demonstrated a significant downregulation of 71 miRNAs, including miR-431, in primary myoblasts from aged mice versus young controls. Subsequent functional analysis confirmed that miR-431 directly binds the 3'UTR of SMAD4 mRNA to repress its expression. Given that SMAD4 acts downstream of TGFβ, it is postulated to indirectly affect metabolic disease pathogenesis via the modulation of insulin resistance or lipid metabolism [30]. While age-related miRNA changes in skeletal muscle are well documented, whether SKM-derived exosomal miRNAs that regulate metabolic organs (e.g., liver, adipose tissue, pancreas) show similar alterations in abundance and diversity remains unknown.

In aged mice, miR-434-3p is significantly upregulated in muscle, and bioinformatic analyses suggest that the pathways it regulates are highly enriched in fatty acid degradation, sphingolipid metabolism, and type 2 diabetes [29]. A core set of seven miRNAs, consistently altered in aged muscle from both humans and mice, exhibits significant enrichment of predicted targets within the insulin signaling pathway [31]. Downregulation of miR-486 leads to a reduction in the inhibition of PTEN, resulting in increased PTEN expression. This, in turn, suppresses the PI3K /Akt/mTOR pathway, a central axis for insulin-mediated glucose uptake and protein synthesis [26, 27]. Age-associated changes in miR-17, miR-19a/b, miR-221, and miR-222 have also been shown to impair insulin sensitivity by modulating PI3K/Akt signaling [26]. The upregulation of miR-34a inhibits ceramide kinase (CERK), leading to the accumulation of sphingolipids. This, in turn, activates the protein phosphatase 2A (PP2A) and c-Jun N-terminal Kinase (JNK) pathways, ultimately impairing insulin signal transduction [27, 32]. These collective findings support the hypothesis that disrupted muscle-derived exosomal miRNA signaling is a key contributor to systemic metabolic dysregulation during aging.

Therapeutic strategies targeting SKM-derived exosomal miRNAs in age-related metabolic diseases

The senescence of SKM disrupts the spectrum and secretion of SKM-derived exosomal miRNAs, which act as key molecular mediators linking SKM to metabolic disorders by dysregulating insulin signaling, lipid metabolism, and inflammatory pathways. Consequently, interventions aimed at this communication system represent a promising frontier for alleviating these conditions. Firstly, the resistance training regimen has been shown to partially reverse the aging phenotype of circulating SKM-derived exosomal miRNAs, providing molecular evidence for exercise intervention [24]. Secondly, vitamin D may improve metabolic health through its anti-inflammatory and myogenic effects [23]. Furthermore, medications that improve insulin sensitivity and antioxidants have also been proven to benefit SKM metabolism [33]. Finally, advanced therapeutic strategies like molecularly targeted treatments also hold significant potential. Studies have proposed using technologies such as antisense oligonucleotides (ASOs), miRNA mimics, or adeno-associated virus (AAV) vectors to therapeutically modulate aberrantly expressed miRNAs in SKM to ameliorate the aging phenotype [28, 34]. Given that these miRNAs are also involved in regulating insulin sensitivity, such strategies hold theoretical potential for correcting the metabolic imbalance caused by SKM-dervied exosomal miRNAs. Moreover, another study found that an unknown "therapeutic factor" present in fetal muscle extracts was also shown to improve muscle function in aged mice, although its precise mechanism remains to be elucidated [35]. However, most of these therapeutic strategies currently remain conceptual or in the preclinical stage, necessitating validation through high-quality research in the future. In summary, SKM aging specifically influences downstream insulin signaling, lipid metabolism, and inflammatory pathways by altering the spectrum and quantity of exosomal miRNAs secreted, thereby establishing a crucial molecular bridge between sarcopenia and metabolic diseases. Interventions targeting this communication system represent a promising future direction for delaying muscle aging and its associated metabolic complications.

Research challenges and future directions

Research on SKM-derived exosomal miRNAs has achieved notable progress, yet some critical issues remain to be addressed. First, the use of diverse exosome isolation methods, such as ultracentrifugation, density ultracentrifugation, size exclusion, and immunoaffinity, has resulted in a lack of standardized protocols. The differing compositions of cargo resulting from these methods significantly compromise the comparability of findings across studies. Future studies should aim to standardize protocols for exosome isolation, characterization, and miRNA quantification. Second, most current studies rely on associative analyses and in vitro experiments, failing to establish a well-defined quantitative impact of SKM-derived exosomal miRNAs on metabolic parameters such as blood glucose and lipid levels. Particular emphasis should be placed on quantifying the regulatory impact of SKM-derived exosomal miRNAs on glucose and lipid metabolism, thereby providing more definitive experimental evidence to inform clinical intervention strategies. Third, SKM-derived exosomal miRNAs are highly susceptible to enzymatic degradation in vivo and are poorly internalized across negatively charged cell membranes, resulting in extremely low bioavailability. Consequently, their therapeutic efficacy depends on efficient and reliable delivery systems that can transport them to the target site. Both viral and non-viral vectors have been explored, yet major challenges remain in achieving adequate targeting, stability, and safety [36]. Fourth, the multi-target nature of SKM-derived exosomal miRNAs poses off-target risks. These limitations have collectively constrained the clinical translation of miRNAs, which explains why no miRNA-based therapeutic has yet received Food and Drug Administration approval. Besides, current studies are methodologically limited. Most findings establish association rather than causation, and the association between altered SKM-derived exosomal miRNAs levels and metabolic phenotypes may be confounded by exosomes derived from other tissues or by systemic factors.

Finally, while rodent and in vitro models have provided valuable mechanistic insights into the role of SKM-derived exosomal miRNAs in metabolic regulation, direct translation to humans remains limited. Most functional evidence supporting SKM-derived exosomal miRNAs in mediating inter-organ communication, modulating signaling pathways, and inducing phenotypic effects following exosome administration originate primarily from mouse models and in vitro cell cultures. These models offer controlled experimental conditions but may not fully recapitulate the complexity of human physiology, including differences in lifespan, metabolic rate, exercise capacity, and systemic crosstalk. Human observational studies linking altered SKM-derived exosomal miRNAs profiles to obesity, type 2 diabetes, or aging provide supportive but largely correlational evidence that lacks functional validation. In vivo human studies demonstrating causal roles for specific SKM-derived exosomal miRNAs through gain- or loss-of-function approaches remain scarce. Future studies should focus on rigorous human validation through longitudinal

interventions, tissue-specific tracking of exosome uptake, and targeted modulation of SKM-derived exosomal miRNAs to confirm therapeutic potential and bridge the gap between animal findings and clinical application.

Conclusions

SKM-derived exosomal miRNAs emerge as crucial mediators of crosstalk between SKM and other metabolic organs, directly regulating processes such as hepatic gluconeogenesis, lipid turnover, and pancreatic islet function.

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Conflict of interest

The authors declare that they have no competing interests.

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